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**Stat3 signaling regulates embryonic stem cell fate in a dose-dependent manner.**

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**Public Summary:**

Embryonic stem cells (ESCs) can be maintained in culture indefinitely while retaining the capacity to become any type of cell in the body, and therefore represent a powerful tool for modeling disease and understanding biological development. However, if the full potential of ESCs in biomedicine is to be realized, it is critical to understand how ESC fate, whether it is self-renewal or differentiation, is determined. Mouse ESCs can be maintained in an undifferentiated state through leukemia inhibitory factor (LIF)-mediated activation of signal transducer and activator of transcription 3 (STAT3). In this study, we discovered a previously unknown function for STAT3 in mouse ESCs, specifically, that STAT3 exhibits a dose-dependent effect in mouse ESC self-renewal and differentiation. While STAT3 activation by LIF generally promotes mouse ESC self-renewal, elevating STAT3 activity over a certain threshold switches STAT3's self-renewal promoting effect into one that induces ESC differentiation towards the trophectoderm lineage. This finding will enhance our ability to control stem cell fate and, in doing so, accelerate developments in regenerative medicine.

**Scientific Abstract:**

Stat3 is essential for mouse embryonic stem cell (mESC) self-renewal mediated by LIF/gp130 receptor signaling. Current understanding of Stat3-mediated ESC self-renewal mechanisms is very limited, and has heretofore been dominated by the view that Stat3 signaling functions in a binary "on/off" manner. Here, in contrast to this binary viewpoint, we demonstrate a contextual, rheostat-like mechanism for Stat3's function in mESCs. Activation and expression levels determine whether Stat3 functions in a self-renewal or a differentiation role in mESCs. We also show that Stat3 induces rapid differentiation of mESCs toward the trophectoderm (TE) lineage when its activation level exceeds certain thresholds. Stat3 induces this differentiation phenotype via induction of Tfap2c and its downstream target Cdx2. Our findings provide a novel concept in the realm of Stat3, self-renewal signaling, and pluripotent stem cell biology. Ultimately, this finding may facilitate the development of conditions for the establishment of authentic non-rodent ESCs.

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